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Rahmani/
01/26/2010

8845-97585 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: 10/581,833	Confirmation No.: 8544
Applicant	: BUFFAT et al.	
Filed	: 13 April 2007	
Art Unit	: 1625	
Examiner	: RAHMANI	
Docket No.	: 8845-97585	
Customer No.: 24628		
Title: MUSCARINIC AGENTS AS THERAPEUTIC COMPOUNDS		

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RULE 312 AMENDMENT

Dear Sir:

The Examiner's Amendment of 28 December 2009 has been carefully reviewed and the following amendments and remarks are made in response thereto:

Amendments to the Claims begin on page **2** of this paper.

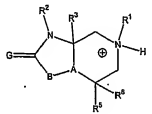
Remarks/Arguments begin on page **14** of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (currently amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is CH or nitrogen;

B is $-CH_2-$, -CHF-, $-CF_2-$, NR_4 or O, with the proviso that when A is N, B is $-CH_2-$, -CHF- or $-CF_2-$;

G is oxygen,

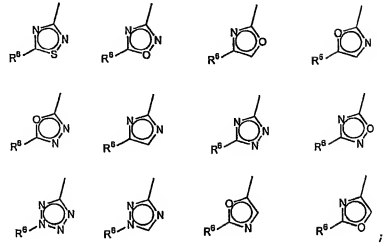
R_1 is hydrogen or C_{1-6} alkyl;

R_2 is C_{1-8} alkyl, $-CH_2$-aryl, CH_2-heterocycle,$-CH_2$-substituted C_5 cycloalkyl, or a $-CH_2$-substituted hetero cycle, each of which may be optionally substituted with one or more of halo, hydroxyl,

C_{1-6} alkyl, C_{1-6} haloalky, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl;

R_3 is hydrogen; cyclobutyl, cyclopropyl, methyl, ethyl, isopropyl, butyl, sec-butyl;

R_5 is a 5-membered unsaturated heterocyclic ring having one of the following structures:



;

R_6 is methyl, aralkyl, arylamino, aralkyl substituted by one or more halo and having a methylene group linking the aryl to the unsaturated 5-membered ring, aralkyl substituted by one or more halo and having an ethylene group linking the aryl to the unsaturated 5-membered ring;or

R_5 may also be C_2-C_4-aralkyl, $-CH_2-O-R_7$ where R_7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_2-C_4 aralkyl which groups may be optionally substituted with fluoro or hydroxy; and

R_8 is hydrogen phenyl or halo-substituted phenyl;

with the proviso that when either R_3 or R_8 is not hydrogen, the other is hydrogen.

2. (cancel)

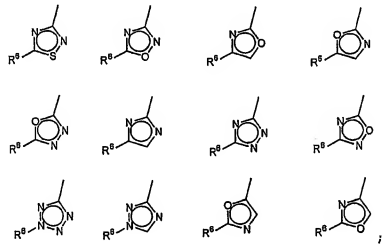
3. (previously presented) A compound according to claim 1, wherein

R_1 is H;

R_2 is -CH_2-aryl optionally substituted with one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkeny1, C_{2-6} alkynyl or C_{2-6} haloalkynyl;

R_3 is hydrogen or cyclobutyl;

R_5 is one of the following 5-membered unsaturated heterocyclic ring structures:



;

R_6 is phenyl, phenylamino substituted by one or more halo, phenylmethyl substituted by one or more halo, or phenethyl substituted by one or more halo; and

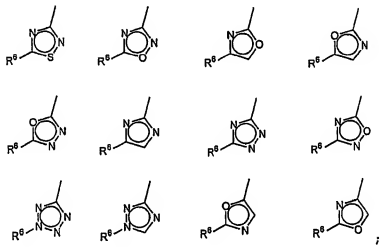
R_8 is hydrogen or a fluoro-substituted phenyl.

4. (previously presented) A compound according to claim 3, wherein

R_2 is $-CH_2-C_6H_5$ or $-CH_2$-heterocyclic aryl each of which may be optionally substituted with one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl;

R_3 is H;

R_5 is one of the following 5-membered unsaturated heterocyclic ring structures:



;

R_6 is a meta chloro-substituted phenylamino, a meta chloro-substituted phenylmethy or a meta chloro-substituted phenethyl; and

R_8 is 3,5-difluorophenyl.

5. (previously presented) A compound according to claim 1, wherein

A is CH;

B is $-CH_2-$;

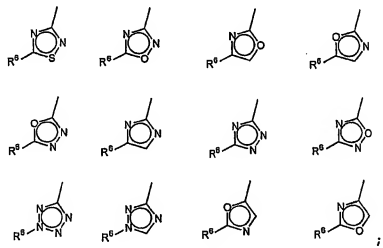
G is oxygen;

R_1 is hydrogen;

R_2 is C_{1-8} alkyl or $-CH_2$-aryl (optionally substituted by one or more of halo, hydroxy, C_{1-8} alkyl, C_{1-6} haloalkyl, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkyny);

R_3 is cyclobutyl or H, and

R_5 is one of the following 5 -membered unsaturated heterocyclic ring structures:



;

6. (previously presented) A compound according to claim 1, in which A is CH;

B is O;

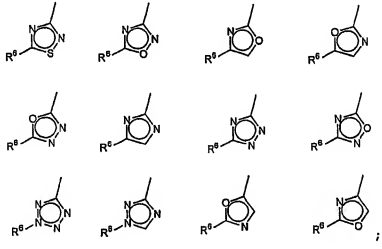
G is oxygen;

R_1 is hydrogen;

R_2 is C_{1-8} alkyl, $-CH_2$-aryl (optionally substituted by one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl);

R_3 is cyclobutyl or H; and

R_5 is $-CH_2$-O-CH_3, $-CH_2$-O-CH_2-CH_2-C_6H_5 or one of the following 5-membered unsaturated heterocyclic ring structures:



7. (previously presented) A compound according to claim 1, wherein .

A is CH;

B is NH;

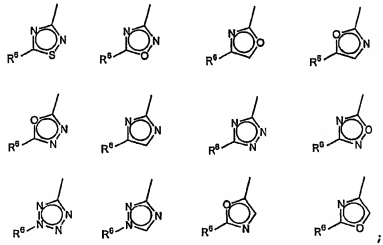
G is oxygen;

R_1 is hydrogen;

R_2 is C_{1-8} alkyl, $-CH_2$-aryl, a $-CH_2$-heterocyclic group or a $-CH_2$-substituted C_5 cycloalkyl (optionally substituted by one or more of halo, hydroxy, C_{l-6} alkyl, C_{l-6} haloalkyl, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl);

R_3 is cyclobutyl or H; and

R_5 is $-CH_2-O-CH_3$, $-CH_2-O-CH_2-CH_2-C_6H_5$ or one of the following 5-membered unsaturated heterocyclic ring structures:



;

8. (previously presented) A compound according to claim 1, wherein

A is N;

B is $-CH_2-$;

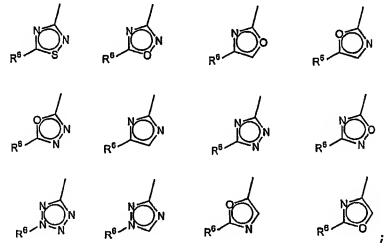
G is oxygen;

R_1 is hydrogen;

R_2 is C_{1-8} alkyl, $-CH_2$-aryl, a $-CH_2$-heterocyclic group or a $-CH_2$-substituted C_5 cycloalkyl (optionally substituted one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl);

R_3 is cyclobutyl or H;

R_5 is one of the following 5-membered unsaturated heterocyclic ring structures:



;

and

R_8 is H or phenyl (optionally substituted with halo).

9. (previously presented) A compound according to claim 1, wherein

A is N;

B is $-CH_2-$;

G is oxygen;

R_1 is hydrogen;

R_2 is C_{1-8} alkyl $-CH_2$-aryl, a $-CH_2$-heterocyclic group or a $-CH_2$-substituted C_5 cycloalkyl (optionally substituted by one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalky, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl);

R_3 is cyclobutyl or H; and

R_5 is $-CH_2-O-CH_3$.

10. (previously presented) A compound according to claim 1,wherein

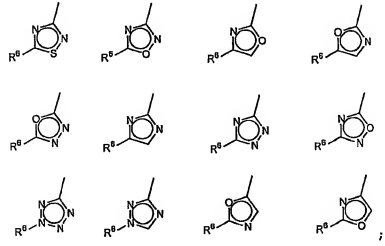
A is N;

B is $-CH_2-$;

R_1 is hydrogen;

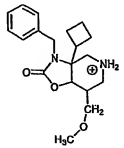
R_3 is hydrogen or cyclobutyl;

R_5 is one of the following 5-membered unsaturated heterocyclic ring structures:



and R_8 is phenyl,3,5-difluorophenyl or H.

11. (original) A compound according to claim 1, having the formula:



12. (previously presented) A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 .

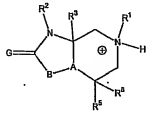
13. (cancel)

14. (currently amended) A method for the manufacture~~of manufacturing~~ of a pharmaceutical for the modification of an acetylcholine or a muscarinic receptor comprising the step of placing the compound of claim 1 into a pharmaceutical composition in a unit dosage form.

15. (currently amended) The method of claim 14, wherein the pharmaceutical is for the treatment of~~is for~~ Alzheimer's disease.

16. (currently amended) A method of modifying a muscarinic acetylcholine receptor or an acetylcholine receptor comprising the administration of a therapeutically effective amount of a compound as claimed in claim 1 to a subject in need thereof.

17. (currently amended) A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is CH or nitrogen;

B is $-CH_2-$, -CHF-, $-CF_2-$, NR_4 or O, with the proviso that when A is N, B is $-CH_2-$, -CHF- or $-CF_2-$;

G is oxygen or =N-CN,

R_1 is hydrogen or C_{1-6} alkyl;

R_2 is hydrogen; C_{1-10} alkyl optionally substituted with C_{1-6} alkoxy or halogen; aralkyl, a $-CH_2$-heterocycle or a $-CH_2-C_5$ cycloalkyl ring each of which may be optionally substituted with one or more of halo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalky, C_{1-8} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl;

R_3 is a cyclic alkyl radical containing from 3-6 carbon atoms or a C_1-C_6 alkyl;

R4 is hydrogen or lower alkyl;

R5 is a 5-membered unsaturated heterocyclic ring optionally substituted by a group selected from~~and~~

~~R6 is~~ lower alkyl; ~~hydrogen; arylamino~~ optionally substituted with one or more of halo, hydroxy, C1-6 alkyl, Cl-6 haloalkyl, C1-6 alkoxy, C1-6 haloalkoxy, C2-6 alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl; aralkyl optionally substituted with one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy,
C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or
C_{2-6} haloalkynyl; or a group of formula:

wherein n is an integer in the range from 1 to 4 and HET is a heterocyclic group optionally substituted with one or more of halo, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl;

or R_5 may also be C_2-C_4-aralkyl, $-CH_2-O-R_7$ where R_7 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_2-C_4 aralkyl which groups may be optionally substituted with fluoro or hydroxy; and

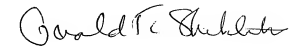
R_8 is hydrogen or aryl (optionally substituted with one or more of halo, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalky, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} haloalkenyl, C_{2-6} alkynyl or C_{2-6} haloalkynyl);
with the proviso that when either R3 or R8 is not hydrogen, the other is hydrogen.

REMARKS / ARGUMENTS

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

With the above amendments and remarks, this application is considered ready for allowance and applicant earnestly solicits an early notice of same. Should the Examiner be of the opinion that a telephone conference would expedite prosecution of the subject application, he/she is respectfully requested to call the undersigned at the below listed number.

Respectfully submitted,



Dated: 22 January 2010

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